

PATENT SPECIFICATION

NO DRAWINGS

Inventor: NORMAN SENIOR

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International Classification:—A01n. A61k, I. C07c.

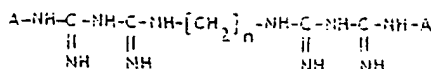
COMPLETE SPECIFICATION

New Biguanide Salts

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

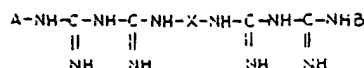
This invention relates to new biguanide salts and more particularly it relates to new bis-biguanide salts which are lipoid soluble and which are useful anti-bacterial agents.

In United Kingdom Patent Specification No. 705,338 there are described and claimed new bactericidal substances of the formula:—



wherein A stands for a phenyl radical which is substituted by alkyl, alkoxy, nitro or halogen, wherein the two A's may be the same or different and wherein n is an integer from 3 to 9 inclusive and wherein the polymethylene chain may be interrupted by oxygen atoms and/or by aromatic nuclei. There are therein described the hydrochloride salts of certain of these new substances.

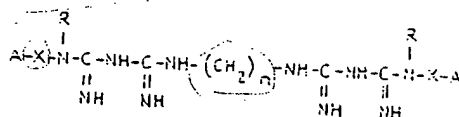
In United Kingdom Patent Specification No. 710,105 there are described and claimed fungicidal and bactericidal compositions which comprise one or more bis-biguanides of the formula:—



wherein A and B stand for aromatic nuclei, the same or different, optionally substituted by one or more hydroxy, halogen, nitro, alkyl or alkoxy radicals and X stands for a bridg-

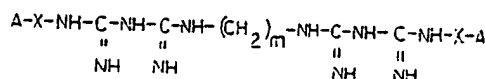
ing group which is a hydrocarbon or a dialkoxy benzene radical of not more than 15 carbon atoms, preferably in the form of their salts, and for each 100 parts by weight of the bis-biguanide between 50 and 20,000 parts by weight of one or more substances of known wetting or detergent properties. There are described therein the hydrochloride and acetate salts of certain of the said bis-biguanides.

In United Kingdom Patent Specification No. 785,937 there are described and claimed new bis-biguanides which are of the formula:—



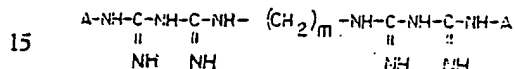
wherein A stands for a phenyl radical which may optionally be substituted by alkyl, alkoxy or nitro groups or by halogen, wherein X stands for an alkylene radical of not more than 3 carbon atoms, wherein R stands for hydrogen or for an alkyl radical or an aralkyl radical, and wherein n is an integer from 2 to 12 inclusive and wherein the polymethylene chain (CH₂)_n may optionally be interrupted by oxygen atoms and/or by aromatic nuclei, and the salts thereof. As suitable salts there are particularly mentioned in the said specification those salts derived from the common inorganic acids for example the hydrochlorides or from the common organic acids for example the acetates, the said salts being soluble in aqueous solvents for example water.

In United Kingdom Patent Application No. 17460/56 (Specification No. 815,925) there are described and claimed new salts of bis-biguanides of the formula:—

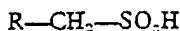


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wherein A stands for a phenyl radical which may optionally be substituted by alkyl radicals or by halogen atoms, and wherein m is an integer from 2—12 inclusive, with hydroxy-
20-alkane sulphonic acids of the formula:—

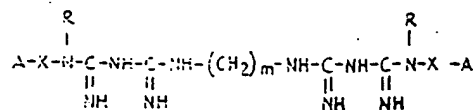


wherein R stands for an alkyl radical substituted by at least one hydroxyl group and which may optionally bear further substituents. It is further stated in both of these specifications that these new bis-biguanide salts are highly soluble in water and are more useful than the known less soluble salts of the said bis-biguanides derived from the common inorganic acids for example the hydrochlorides or from the common organic acids for example the acetates.

35 In none of the above specifications have there been specifically described lipid soluble salts of the bis-biguanides of the kind stated with fatty acids having finite solubility in water.

We have now found that certain bis-biguanides of the kind stated form salts with fatty acids having finite solubility in water and that these salts have properties entirely different from those of the bis-biguanide salts previously described. The new salts are of high lipoid solubility and low water solubility. In spite of the low degree of water solubility these salts possess antibacterial and antifungal action by reason of their solubility in oil and, possibly because of their low solubility in water, they are non-irritant. They are thus of value in the treatment of infections of bacterial and/or fungal origin in general and more particularly they are of superior value to the known bis-biguanide salts mentioned above in the treatment of infections of bacterial and/or fungal origin in circumstances which require penetration of the active agent into or through lipoid material and/or a measure of water-repellance.

Thus according to the invention we provide new salts of bis-biguanides of the formula:— 60



wherein A stands for a phenyl radical which may be substituted by alkyl, alkoxy, or nitro groups or by halogen, wherein R stands for hydrogen or for an alkyl radical or an aralkyl radical, wherein X stands for a direct linkage or for an alkylene radical of not more than 3 carbon atoms, wherein m is an integer from 2 to 12 inclusive and wherein the polymethylene chain $(CH_2)_m$ may optionally be interrupted by oxygen atoms and/or by aromatic nuclei, with C_{60} — C_{60} , aliphatic and olefinic acids, and those C-substituted derivatives thereof which are monohydroxy, carbonyl or ester derivatives thereof.

As suitable bis-biguanides for use in the salts of the invention there may be mentioned those bis-biguanides which are disclosed in said United Kingdom Patent Specifications Nos. 705,838 and 785,937, and in particular those of the above formula wherein A stands for a halogen-substituted phenyl or benzyl group, and still more particularly there may be mentioned 1:6-di-(N₁:N₁')-p-chlorophenybiguanido-N₂:N₂')-hexane, also known as Chlorhexidine, and 1:6-di-(N₁:N₁')-p-chlorobenzylbiguanido-N₂:N₂')-hexane.

The C_6 — C_{22} aliphatic and olefinic acids and said C-substituted derivatives thereof may be of natural or synthetic origin. 90

As suitable aliphatic acids for use in the salts of the invention there may be mentioned straight-chain C_6 — C_{22} aliphatic acids for example arachidic acid, stearic acid, palmitic acid and lauric acid, and branched chain C_6 — C_{22} aliphatic acids.

As suitable olefinic acids for use in the salts of the invention there may be mentioned straight chain C_8 — C_{22} olefinic acids for example oleic acid, linoleic acid and linolenic acid.

As suitable C-substituted derivatives of the said acids there may be mentioned for example those wherein the substituent is a carbonyl group or an ester thereof with, for example, a monohydric alcohol or with a partially esterified polyhydric alcohol, for example with a glycerol di-ester.

As a suitable manohydroxy derivative of the said acid there may be mentioned, for example, ricinoleic acid. 110

According to a further feature of the invention we provide a process for the manufacture of the said new bis-biguanide salts which comprises interaction of a $C_{12}-C_{20}$ aliphatic

or olefinic acid or a C-substituted derivative thereof, or a salt thereof, with a bis-biguanide of the above-stated formula or a salt thereof.

The process, in the case where the C_6-C_{12} aliphatic or olefinic acid or a C-substituted derivative thereof is interacted with the bis-biguanide base, may conveniently be carried out in a liquid medium for example in an alcoholic medium. Alternatively a salt of the said acid, for example an alkali salt, for example a sodium salt, may be interacted in an aqueous medium with a water soluble salt of the bis-biguanide for example a salt derived from the common inorganic acids for example a hydrochloride or from the common organic acids for example an acetate or from the polyhydroxycarboxylic acids for example a gluconate.

As stated above it has been found that the salts of the invention have high lipid-solubility and low water-solubility and are superior as antibacterial and antifungal agents to known bis-biguanide salts in circumstances which require penetration of the active agent into or through lipid material and/or a measure of water-repellance.

Thus according to yet a further feature of the invention we provide antimicrobial and antifungal compositions comprising as active antimicrobial and antifungal agent one or more of the new salts of the invention in admixture with an inert diluent or carrier.

As examples of such compositions there may be mentioned in particular compositions suitable for topical application in the pharmaceutical and veterinary fields. One advantage of the compositions of the invention for topical application over similar compositions comprising as active ingredient other known bis-biguanide salts lies in their reduced irritancy to delicate tissues. It has been found for example that Chlorhexidine diacetate is non-irritant when applied to tissues. The compositions of the invention are thus ideal for use for example in the treatment of eye infections and to prevent infection in cases of eye injury and also in the treatment of infections of the ear. As a further example of such use there may be mentioned the treatment of bovine mastitis in which it is essential that the medicament used be non-irritant. Another advantage possessed by such compositions derives from the preferential lipid solubility of the active agents thereof, which property assists penetration into and fixation by body tissues while protecting against too rapid dilution by and diffusion into any aqueous phase which may also be present. In the case of mastitis cited above for example it is also advantageous for the active ingredient to be soluble in the oil phase of the milk.

Suitable compositions of the invention for pharmaceutical and veterinary use by topical application include solutions, suspensions,

ointments, powders and the like. The salts of the invention are preferentially wetted by organic liquids rather than by water and their partition as between water and water-immiscible organic liquids is generally speaking substantially in favour of the non-aqueous phase. The said salts have a relatively high solubility in lipid and lipophilic materials, both natural and synthetic, for example in natural oils or fats of vegetable origin for example castor oil, arachis oil, sesame oil and palm oil, in fats of animal origin for example prepared lard, in higher aliphatic esters, alcohols, hydrocarbons and the like. Many of the excipients in standard pharmaceutical and veterinary formulations, particularly for topical use, are of this nature and such vehicles are particularly appropriate for the new salts of the invention. The solubility of these salts in oils and their preferential solubility in the oil phase of aqueous emulsions are of special value in the prevention of skin infections in that the new salts are absorbed into the subcutaneous layers as the oil is made to penetrate by infiltration. The resistance to attack by aqueous media afforded by the resistance to wetting both of the new salts and of the oil formulations containing them also plays an important role in the efficacy of compositions of this type. Because of such resistance properties the said salts and the compositions thereof are also of value in the treatment of intestinal infections due to bacteria and fungi.

The salts and compositions of the invention may be used in conjunction with or may contain other known antimicrobial and antifungal agents for example other known bis-biguanide salts not possessing lipid solubility.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

One part of 1:6-di- $(N_1:N_1'$ -p-chlorophenyldiguanido- $N_2:N_2'$)-hexane diacetate in solution in 20 parts of water at 60°C. is added slowly with stirring to a solution of one part of sodium stearate in 50 parts of water at 60°C. The resulting precipitate of 1:6-di- $(N_1:N_1'$ -p-chlorophenyldiguanido- $N_2:N_2'$)-hexane distearate is filtered, washed with hot water and dried.

EXAMPLE 2

To a solution of 4 parts of lauric acid in 50 parts of ethanol at 60°C. there are added 5 parts of 1:6-di- $(N_1:N_1'$ -p-chlorophenyldiguanido- $N_2:N_2'$)-hexane and the suspension is refluxed for 2 hours or until salt formation is complete. The mixture is cooled in ice, filtered and washed and there is thus formed 1:6-di- $(N_1:N_1'$ -p-chlorophenyldiguanido- $N_2:N_2'$)-hexane dilaurate.

EXAMPLE 3

To a solution of 0.56 part of oleic acid in 99 parts of castor oil there is added 0.5 part of 1:6-di- $(N_1:N_1'$ -p-chlorophenyldiguanido-

$N_2:N_6$)-hexane in fine powder. The mixture is stirred at 60°C. for 15 minutes and it is then cooled and filtered to give a solution of 1 part of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane dioleate in 100 parts of castor oil.

EXAMPLE 4

To 100 parts of castor oil sterilised by heating to 150°C. for one hour, followed by cooling to 60°C. there is added 0.5 part of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane distearate. The mixture is stirred until a clear solution is formed. There is thus obtained a solution suitable for use as antiseptic eye drops.

EXAMPLE 5

To a solution of 2 parts of polyoxyethylene (20) sorbitan monooleate in 70 parts of castor oil there are added 20 parts of finely powdered 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane dioleate and the mixture is stirred until uniform. The composition thus formed is suitable for the treatment of bacterial and fungal infections of the ear.

EXAMPLE 6

To a solution of 5 parts of oleic acid in 90 parts of castor oil at 70°C. there are added 5 parts of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane and the mixture is stirred for 15 minutes, cooled and homogenised to give a uniform dispersion. The product so obtained is suitable for oral or rectal administration in the treatment of bacterial infections of the intestine.

EXAMPLE 7

A solution of 10 parts of yellow soft paraffin and 5 parts of a polyoxyethylene sorbitan mono-oleate in 60 parts of castor oil is sterilised by heating to 150°C. for one hour and is then cooled to 50°C. To this is added 25 parts of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane dioleate in fine powder. The mixture thus obtained may be used as an intramammary cream suitable for the treatment of bovine mastitis.

EXAMPLE 8

0.5 part of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane linoleate is dissolved with stirring in a mixture of 20 parts of castor oil and 8 parts of cetostearyl alcohol at 50°C. and to this is added a solution of 0.3 part of Cetrimide in 70 parts of water at the same temperature. Stirring is continued to form an emulsion which is adjusted to a total of 100 parts by the addition of warm water, homogenised and cooled. The oil-in-water cream thus formed is suitable for topical use as a preventative of and as a treatment for bacterial infections of the skin.

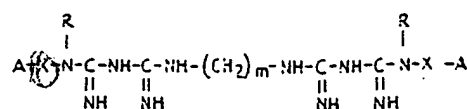
EXAMPLE 9

To a molten mixture of 10 parts of castor oil, 7 parts of stearic acid and 2 parts of cetostearyl alcohol at 70°C. there is added with stirring 0.5 part of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane and

stirring and heating are continued until a uniform solution is obtained. To this is added a solution of 0.5 part of Cetrimide in 80 parts of water and the mixture is stirred and homogenised to give an antiseptic cream suitable for medical or veterinary purposes.

WHAT WE CLAIM IS:—

1. Salts of bis-biguanides of the formula:—



wherein A stands for a phenyl radical which may be substituted by alkyl, alkoxy, or nitro groups or by halogen, wherein R stands for hydrogen or for an alkyl radical or an aralkyl radical, wherein X stands for a direct linkage or for an alkylene radical of not more than 3 carbon atoms, wherein m is an integer from 2 to 12 inclusive, and wherein the polymethylene chain $(\text{CH}_2)_m$ may optionally be interrupted by oxygen atoms and/or by aromatic nuclei, with C_6 — C_{22} aliphatic or olefinic acids or those C-substituted derivatives thereof which are monohydroxy, carboxy or ester derivatives thereof.

2. Salts, as claimed in Claim 1, of bis-biguanides of the formula stated in Claim 1 wherein A stands for a halogen-substituted phenyl or benzyl group.

3. Salts, as claimed in Claim 1, of 1:6-di- $(N_1:N_4$ - p -chlorophenyldiguanido- $N_2:N_6$)-hexane.

4. Salts, as claimed in Claim 1, of 1:6-di- $(N_1:N_4$ - p -chlorobenzylbiguanido- $N_2:N_6$)-hexane.

5. Salts, as claimed in Claims 1—4, the acid component of which is arachidic acid, steric acid, palmitic acid, lauric acid, or other straight-chain C_6 — C_{22} aliphatic acid.

6. Salts, as claimed in Claims 1—4, the acid component of which is oleic acid, linoleic acid, linolenic acid, or other straight-chain C_6 — C_{22} olefinic acid.

7. Salts, as claimed in Claims 1—4, wherein the acid component is an ester of a carboxy-substituted C_6 — C_{22} aliphatic or olefinic acid with a monohydric alcohol or with a partially esterified polyhydric alcohol, for example with a glycerol di-ester.

8. Salts, as claimed in Claims 1—4, wherein the acid component is ricinoleic acid.

9. Process for the manufacture of the bis-biguanide salts claimed in Claims 1—8 which comprises interaction of a C_6 — C_{22} aliphatic or olefinic acid or a C-substituted derivative thereof, or a salt thereof, with a bis-biguanide of the formula stated in Claim 1, or a salt thereof.

10. Antimicrobial and antifungal compositions comprising as active antimicrobial and antifungal agent one or more of the salts

claimed in Claims 1—8, admixture with an inert diluent or carrier.

11. Salts, as claimed in Claims 1—8, as hereinbefore defined and especially with reference to the foregoing Examples 1 and 2.

12. Process, as claimed in Claim 9, as hereinbefore defined and especially with re-

ference to the foregoing Examples 1 and 2.

13. Compositions, as claimed in Claim 10, as hereinbefore defined and especially with reference to the foregoing Examples 3—9 inclusive.

ALFRED O. BALL,
Agent for the Applicants.

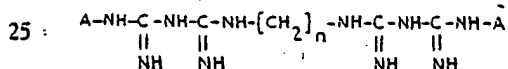
PROVISIONAL SPECIFICATION

New Biguanide Salts

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare this invention to be described in the following statement:—

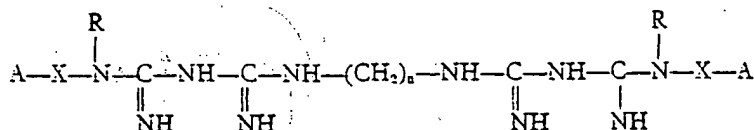
This invention relates to new biguanide salts and more particularly it relates to new bis-biguanide salts which are lipid soluble and which are useful anti-bacterial agents.

In United Kingdom Patent Specification No. 705,838 there are described and claimed new bactericidal substances of the formula:—



wherein A stands for a phenyl radical which is substituted by alkyl, alkoxy, nitro or halogen, wherein the two A's may be the same or different and wherein n is an integer from 3 to 9 inclusive and wherein the polymethylene chain may be interrupted by oxygen atoms and/or by aromatic nuclei. There are therein described the hydrochloride salts of certain of these new substances.

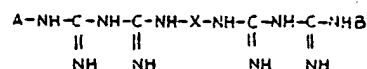
In United Kingdom Patent Specification



wherein A stands for a phenyl radical which may optionally be substituted by alkyl, alkoxy or nitro groups or by halogen, wherein X stands for an alkylene radical of not more than 3 carbon atoms, wherein R stands for hydrogen or for an alkyl radical or an aralkyl radical, and wherein n is an integer from 2 to 12 inclusive and wherein the polymethylene chain $(\text{CH}_2)_n$ may optionally be interrupted by oxygen atoms and/or by aromatic nuclei, and the salts thereof. As suitable salts there are particularly mentioned in the said specification those salts derived from the common inorganic acids for example the hydrochlorides or from the common organic acids for example the acetates, the said salts being soluble in aqueous solvents for example water.

In United Kingdom Patent Application No. 17460/56 (Serial No. 815,925) there are

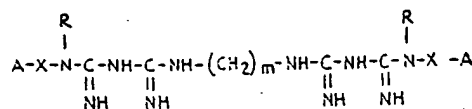
No. 710,105 there are described and claimed fungicidal and bactericidal compositions which comprise one or more bis-biguanides of the formula:—



wherein A and B stand for aromatic nuclei, the same or different, optionally substituted by one or more hydroxy, halogen, nitro, alkyl or alkoxy radicals and X stands for a bridging group which is a hydrocarbon or a dialkoxy benzene radical of not more than 15 carbon atoms, preferably in the form of their salts, and for each 100 parts by weight of the bis-biguanide between 50 and 20,000 parts by weight of one or more substances of known wetting or detergent properties. There are described therein the hydrochloride and acetate salts of certain of the said bis-biguanides.

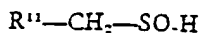
In United Kingdom Patent Specification No. 785,937 there are described and claimed new bis-biguanides which are of the formula:—

described and claimed new salts of bis-biguanides of the formula:—



wherein A stands for a phenyl radical which may be substituted by alkyl, alkoxy, or nitro groups or by halogen and wherein the two A's may be the same or different, wherein R and R', which may be the same or different, stand for hydrogen or for an alkyl radical or an aralkyl radical, wherein X and X', which may be the same or different, stand for a direct linkage or for an alkylene radical of not more than 3 carbon atoms, wherein m is an

integer i , 2 to 12 inclusive and wherein the polymethylene chain $(CH_2)_m$ may optionally be interrupted for example by oxygen atoms and/or by aromatic nuclei, with polyhydroxycarboxylic acids and in United Kingdom Patent Application No. 17461/56 (Serial No. 815,800) there are described and claimed new salts of bis-biguanides of the same formula with hydroxyalkane sulphonic acids of the formula:—



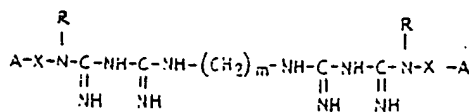
wherein R^{11} stands for an alkyl radical substituted by at least one hydroxyl group and which may optionally bear further substituents.

It is further stated in both of these applications that these new bis-biguanides salts are highly soluble in water and are more useful than the known less soluble salts of the said bis-biguanides derived from the common inorganic acids for example the hydrochlorides or from the common organic acids for example the acetates.

In none of the above specifications have there been specifically described lipid soluble salts of the bis-biguanides of the kind stated with fatty acids having finite solubility in water.

We have now found that bis-biguanides of the kind stated form salts with fatty acids having finite solubility in water and that these salts have properties entirely different from those of the bis-biguanide salts previously described. The new salts are of high lipid solubility and low water solubility. In spite of the low degree of water solubility these salts possess antibacterial and antifungal action by reason of their solubility in oil and, possibly because of their low solubility in water, they are non-irritant. They are thus of value in the treatment of infections of bacterial and/or fungal origin in general and more particularly they are of superior value to the known bis-biguanide salts mentioned above in the treatment of infections of bacterial and/or fungal origin in circumstances which require penetration of the active agent into or through lipid material and/or a measure of water-repellance.

Thus according to the invention we provide new salts of bis-biguanides of the formula:—



wherein A stands for a phenyl radical which may be substituted by alkyl, alkoxy, or nitro groups or by halogen and wherein the two A's may be the same or different, wherein R and R^1 , which may be the same or different, stand for hydrogen or for an alkyl radical or an

aralkyl radical, wherein X and X^1 , which may be the same or different, stand for a direct linkage or for an alkylene radical or not more than 3 carbon atoms, wherein m is an integer from 2 to 12 inclusive and wherein the polymethylene chain $(CH_2)_m$ may optionally be interrupted for example by oxygen atoms and/or by aromatic nuclei, with C_6-C_{22} aliphatic and olefinic acids and C-substituted derivatives thereof.

As suitable bis-biguanides for use in the salts of the invention there may be mentioned in particular those of the above formula wherein A stands for a halogen-substituted phenyl or benzyl group, and still more particularly there may be mentioned 1:6-di- $N_1:N_1'$ -*p*-chlorophenylbiguanido- $N_2:N_2'$ -hexane, also known as Chlorhexidine, and 1:6-di- $(N_1:N_1'$ -*p*-chlorobenzylbiguanido- $N_2:N_2'$ -hexane.

The C_6-C_{22} aliphatic and olefinic acids and C-substituted derivatives thereof may be of natural or of synthetic origin.

As suitable aliphatic acids for use in the salts of the invention there may be mentioned straight-chain C_6-C_{22} aliphatic acids for example arachidic acid, stearic acid, palmitic acid and lauric acid, and branched chain C_6-C_{22} aliphatic acids.

As suitable olefinic acids for use in the salts of the invention there may be mentioned straight chain C_6-C_{22} olefinic acids for example oleic acid, linoleic acid and linolenic acid.

As suitable C-substituted derivatives of the said acids there may be mentioned for example those wherein the substituent is a carbonyl group or a derivative thereof for example an ester thereof with, for example, a monohydric alcohol or with a polyhydric alcohol residue, for example with a glycerol di-ester residue.

As suitable C-substituted derivatives of the said acids there may further be mentioned for example those wherein the substituent is a hydroxyl radical for example ricinoleic acid or a derivative thereof.

According to a further feature of the invention we provide a process for the manufacture of the said new bis-biguanide salts which comprises interaction of a C_6-C_{22} aliphatic or olefinic acid or a C-substituted derivative thereof, or a salt thereof, with a bis-biguanide of the above-stated formula or a salt thereof.

The process, in the case where the C_6-C_{22} aliphatic or olefinic acid or a C-substituted derivative thereof is interacted with the bis-biguanide base, may conveniently be carried out in a liquid medium for example in an alcoholic medium. Alternatively a salt of the said acid, for example an alkali salt, for example a sodium salt, may be interacted in an aqueous medium with a water soluble salt of the bis-biguanide for example a salt derived from the common inorganic acids for example

a hydrochloride or from the common organic acids for example an acetate or from the polyhydroxycarboxylic acids for example a gluconate.

5 As stated above it has been found that the salts of the invention high above lipid-solubility and low water-solubility and are superior as antibacterial and antifungal agents to known bis-biguanide salts in circumstances
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Thus according to yet a further feature of the invention we provide antimicrobial and
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Suitable compositions of the invention for pharmaceutical and veterinary use by topical
50 application include solutions, suspensions, ointments, powders and the like. The salts of the invention are preferentially wetted by organic liquids rather than by water and their partition as between water and water-immiscible organic liquids is generally speaking
55 substantially in favour of the non-aqueous phase. The said salts have a relatively high solubility in lipid and lipophilic materials, both natural and synthetic, for example in
60 natural oils or fats of vegetable origin for example castor oil, arachis oil, sesame oil and palm oil, in fats of animal origin for example prepared lard, in higher aliphatic esters, alcohols, hydrocarbons and the like. Many of
65 the excipients in standard pharmaceutical and

veterinary formulaions, particularly for topical use, are of this nature and such vehicles are particularly appropriate for the new salts of the invention. The solubility of these salts in oils and their preferential solubility in the oil phase of aqueous emulsions are of special value in the prevention of skin infections in that the new salts are absorbed into the subcutaneous layers as the oil is made to penetrate by infraction. The resistance to attack
70 by aqueous media afforded by the resistance to wetting both of the new salts and of the oil formulations containing them also plays an important role in the efficacy of compositions of this type. Because of such resistance
75 properties the said salts and the compositions thereof are also of value in the treatment of intestinal infections due to bacteria and fungi.

The salts and compositions of the invention may be used in conjunction with or may contain other known antimicrobial and antifungal agents for example other known bis-biguanide salts not possessing lipid solubility.

The invention is illustrated but not limited by the following Examples in which the parts
80 are by weight:—

EXAMPLE 1

One part of 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane diacetate in solution in 20 parts of water at 60°C. is added
85 slowly with stirring to a solution of one part of sodium stearate in 50 parts of water at 60°C. The resulting precipitate of 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane distearate is filtered, washed with hot
90 water and dried.

EXAMPLE 2

To a solution of 4 parts of lauric acid in 50 parts of ethanol at 60°C. there are added
95 5 parts of 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane and the suspension is refluxed for 2 hours or until salt formation is complete. The mixture is cooled in ice, filtered and washed and there is thus
100 formed 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane dilaurate.

EXAMPLE 3

To a solution of 0.56 part of oleic acid in 99 parts of castor oil there is added 0.5 part
105 of 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane in fine powder. The mixture is stirred at 60°C. for 15 minutes and it is then cooled and filtered to give a solution of 1 part of 1:6-di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane dioleate in
110 100 parts of castor oil.

EXAMPLE 4

To 100 parts of castor oil sterilised by heating to 150°C. for one hour, followed by cooling to 60°C. there is added 0.5 part of 1:6-
115 di-(N₁:N₁¹-p-chlorophenyldiguanido-N₂:N₂¹)-hexane distearate. The mixture is stirred until a clear solution is formed. There is thus obtained a solution suitable for use as
120 antiseptic eye drops.

EXAMPLE 5

To a solution of 2 parts of polyoxyethylene (20) sorbitan monooleate in 70 parts of castor oil there are added 20 parts of finely powdered 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane dioleate and the mixture is stirred until uniform. The composition thus formed is suitable for the treatment of bacterial and fungal infections of the ear.

EXAMPLE 6

To a solution of 5 parts of oleic acid in 90 parts of castor oil at 70°C. there are added 5 parts of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane and the mixture is stirred for 15 minutes, cooled and homogenised to give a uniform dispersion. The product so obtained is suitable for oral or rectal administration in the treatment of bacterial infections of the intestines.

EXAMPLE 7

A solution of 10 parts of yellow soft paraffin and 5 parts of a polyoxyethylene sorbitan mono-oleate in 60 parts of castor oil is sterilised by heating to 150°C. for one hour and is then cooled to 60°C. To this is added 25 parts of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane dioleate in fine powder. The mixture thus obtained may be used as an intrammary cream suitable for the treatment of bovine mastitis.

EXAMPLE 8

0.5 part of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane linoleate is dissolved with stirring in a mixture of 20 parts of castor oil and 8 parts of cetostearyl alcohol at 60°C. and to this is added a solution of 0.3 part of Cetrimide in 70 parts of

water at the same temperature. Stirring is continued to form an emulsion which is adjusted to a total of 100 parts by the addition of warm water, homogenised and cooled. The oil-in-water cream thus formed is suitable for topical use as a preventative of and as a treatment for bacterial infections of the skin.

EXAMPLE 9

To a molten mixture of 10 parts of castor oil, 7 parts of stearic acid and 2 parts of cetostearyl alcohol at 70°C. there is added with stirring 0.5 part of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane and stirring and heating are continued until a uniform solution is obtained. To this is added a solution of 0.5 part of Cetrimide in 80 parts of water and the mixture is stirred and homogenised to give an antiseptic cream suitable for medical or veterinary purposes.

EXAMPLE 10

A solution of 0.5 part of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane di-D-glucuronate in 70 parts of water at 60°C. is added to a fused mixture at 60°C. of 15 parts of arachis oil, 9 parts of cetostearyl alcohol and 1 part of Cetomacrogol 1000 B.P.C. containing 0.2 part of 1:6-di-($N_1:N_1'$ -*p*-chlorophenyldiguanido- $N_2:N_2'$)-hexane dipalmitate. The mixture is stirred to form an emulsion, adjusted to 100 parts by the incorporation of warm water, homogenised and cooled to give a cream suitable for topical use for the prevention and treatment of bacterial infections of the skin.

ALFRED O. BALL,
Agent for the Applicants.